IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Wechs

Art Unit:

Serial No. 10/588,016

Examiner:

Filed: August 1, 2006

For: HIGH-FLUX DIALYSIS MEMBRANE WITH IMPROVED SEPARATION BEHAVIOUR

PETITION UNDER RULE 182

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Request

By this Petition under Rule 182, Applicant requests:

1. Entry of the attached English translation of the priority document;

2. Entry of the attached Preliminary Amendment;

3. Correction of the filing receipt to reflect the correct title of the application as "Integrally Asymmetric Membrane, Method for its Production and its Use."

Attachments

Attached hereto, please find:

1. The correct English translation;

2. A Preliminary Amendment;

3. Fees, which may be charged to Deposit Account No. 082447, required under Rule 17(f) [Petition fee] and Rule 492(i) [filing translation after 30 month period].

Discussion

On July 31, 2007, the undersigned learned that the English translation file in the above captioned application was incorrect.

The above captioned application claims priority from PCT/EP05/01507 (filed February 15, 2005) and German 10 2004 008 219.7 (filed February 19, 2004). Both of the priority applications are German language documents.

On June 30, 2006, the undersigned received instructions from Applicant to file the US national application for PCT/EP05/01507. Included with those instructions was an English translation. This English translation, we now understand, was incorrect.

The incorrect translation was filed with the USPTO on August 1, 2006.

On April 23, 2007, the undersigned received from the USPTO, a 'Notice of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.495.'

On July 27, 2007, the undersigned received a 'Notice of Publication of Application.'

On July 30, 2007, the undersigned sent a copy of the published application to Applicant.

On July 31, 2007, Applicant informed the undersigned about the incorrect translation.

The undersigned then conducted an investigation of the file and discovered that the translation filed was the same as the one received from the Applicant on June 30, 2006.

The undersigned then called the USPTO's PCT Help Desk and spoke with Jim Lashora. After explaining the situation, the undersigned was instructed to file the instant petition.

Accordingly, the undersigned respectfully requests that the correct English translation of the priority document be entered in the instant application, along with the attached Preliminary Amendment, and that the Filing Receipt be correct to reflect the proper title of the application. Any additional fees may be charged to Deposit Account No. 082447.

Respectfully submitted,

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Integrally Asymmetric Membrane, Method for its Production, and its Use

Description

The present invention relates to an integrally asymmetric membrane, a method for its production, and its use.

Integrally asymmetric membranes and methods for their production are known, and described in, for example, EP 0 828 553 B1, EP 0361 085 B1 and EP 0168 783 B1. In the cited patent specifications and the present invention, an integrally asymmetric membrane is understood to be one having a separating layer and a supporting layer, the separating and supporting layers consisting of the same material and being formed simultaneously with the production of the membrane, as a result of which both layers are bound together as an integral unit. Such membranes are used for separation operations in, for example, the medical field (e.g., in hemodialysis) and the food industry (e.g., for dealcoholisation of drinks).

In contrast to integrally asymmetric membranes, composite membranes have a multilayer structure, in which a dense separating layer is applied on a previously produced (micro)porous supporting layer or supporting membrane in a subsequent, i.e. separate, process step such as coating with a film-forming polymer, or grafting with a monomer forming this polymer. This separate process step is un-

necessary in the production of an integrally asymmetric membrane, in the preparation of which the separating and support layers are generated merely by bringing the polymer solution used to form the shaped membrane into contact with a precipitant system.

The essential criteria in the evaluation of a membrane are its separation characteristics, i.e., its cutoff and its separation efficiency. The cutoff is here understood to be the exclusion limit for a molecule or substance of a particular size, which depends on the diameter of the pores in the separating layer of the membrane. The separation efficiency provides information on the selectivity of the membrane.

In hemodialysis, for example, it is important that loss of high-molecular proteins such as albumin (of molecular weight 65 000 daltons) from the blood of a dialysis patient is minimised. In other words, the membrane should have a sieving coefficient SC for albumin that is as close as possible to 0.000. At the same time, the membrane should be as highly permeable as possible not only to urea and low-molecular uremic toxins, such as creatinine or phosphate, but also to "middle molecules", i.e. proteins of medium molecular weight, such as β_2-microglobulin. This means that the membrane should have an SC for β_2-microglobulin that is ideally as close as possible to 1.000.

However, these requirements are not satisfactorily fulfilled by currently known membranes. Currently known membranes have an SC for β_2-microglobulin or for cytochrome c, often used as a marker molecule for β_2-microglobulin, that is significantly lower than 1. Simultaneously, the sieving coefficients obtained for albumin, while lying close to zero, are still often significantly higher than for the natural kidney. A membrane produced according to Example 13 of EP 828 553, for example, has a sieving coefficient for cytochrome c of 0.75 and a sieving coefficient for albumin of 0.05. The membranes disclosed in EP 0 168 783 B1, although having a

low sieving coefficient (0.005) for albumin, do not achieve satisfactory separation efficiencies for middle molecules.

A need still exists, therefore, for integrally asymmetric membranes with improved separation efficiency.

The object of the present invention is therefore to at least reduce the disadvantages described above.

This object is achieved by a method for producing an integrally asymmetric membrane with at least one separating layer and a supporting layer adjoining the separating layer, comprising the following steps:

a) preparation of a spinning solution comprising a membrane-forming polymer and a solvent system,
b) conversion of the spinning solution by means of a forming device into a shaped object with a first and a second surface,
c) bringing of the first and/or second surface into contact with a precipitant system, resulting in the formation of a membrane that has a separating layer on the first and/or second surface, and
d) washing and, if necessary, drying of the membrane,

characterised in that in step c) the precipitant system comprises a polyelectrolyte with negative fixed charges.

Surprisingly, the method of the invention allows production of integrally asymmetric membranes that, in comparative with membranes produced by known methods, have significantly higher separation efficiency between middle molecules, such as cytochrome c, and high-molecular proteins, such as albumin. In preferred embodiments of the method of the invention, which will be described in detail below, membranes can be produced with sieving coefficients SC_{CC} for cytochrome c of up

to 1.000 and simultaneously sieving coefficients SC_{Alb} for bovine serum down to 0.000.

On account of the sharp separation characteristics and the excellent retention of albumin, the structure or separating layer of the membrane of the invention can be made more open without producing an unwanted increase in the sieving coefficients for bovine serum albumin. This simultaneously allows a further increase in the sieving coefficients for cytochrome c, and elimination of low-molecular proteins such as β_2-microglobulin can be further improved. Surprisingly, a large number of embodiments of the method of the invention provide integrally asymmetric membranes that show not only the increased selectivity described above, but also increased permeability in the form of an increased ultrafiltration rate, as is shown in the examples. Moreover, the integrally asymmetric membranes produced by the method of the invention generally possess improved pyrogen retention. It must also be pointed out that the method of the invention can be executed with only very slight technical changes in the known methods for producing membranes, i.e. by the use of a precipitant system, used in any case, to which the only addition is a polyelectrolyte with negative fixed charges.

In the context of the present invention, a polyelectrolyte with negative fixed charges is a polymer that contains functional groups with negative charges, or that can form such groups in an adequately basic medium, the functional groups being covalently bound to the polymer. This means that the negative charges are also necessarily covalent, i.e. strongly bound to the polymer.

It is important that the polyelectrolyte with negative fixed charges used in the method of the invention actually be a polymer with the properties defined above, i.e. a molecule in which a large number of monomer units, preferably at least a few hundred and especially preferably at least a few thousand, are covalently bound, resulting in a molecular weight that is preferably > 7 000 daltons and especially

preferably > 70 000 daltons. The use in the precipitant system of low-molecular electrolytes with negative fixed charges, such as citric acid, whose three acid groups can form three negative ions, results in membranes that do not show increased separation efficiency. It is also important that the polyelectrolyte used in the method of the invention possess negative fixed charges. If polyelectrolytes with positive fixed charges, such as a copolymer of vinylpyrrolidone and methacrylamide propyl trimethyl ammonium chloride, are added to the interior filler, the resulting membranes again show no increased separation efficiency.

Suitable polyelectrolytes with negative fixed charge in the precipitant system include, for example, polymers with phenol groups. In a preferred embodiment of the method of the invention, the precipitant system in step c) comprises a polyelectrolyte with negative fixed charges chosen from the group of polyphosphoric acids, polysulfonic acids, or polycarboxylic acids, and particularly, in the last case, homo- and copolymers of acrylic acid. In regard to improvement of the separation behaviour of the membrane produced by the method of the invention,

- partially crosslinked acrylic acids,
- copolymers of methacrylic acid and methyl methacrylate,
- copolymers of acrylic acid and vinylpyrrolidone and
- copolymers of acrylic acid, vinylpyrrolidone and lauryl methacrylate

have proved especially effective.

A particularly marked increase in separation efficiency between middle molecules, such as cytochrome c, and high-molecular proteins, such as albumin, is observed when a polyelectrolyte with negative fixed charges is chosen that is completely soluble in the precipitant system used to form the separating layer, but not in the individual components of the precipitant system.

Moreover, a particularly marked increase in separation efficiency between middle molecules and high-molecular proteins is observed when the polyelectrolyte with

negative fixed charges used for the method of the invention is so chosen that it preferably precipitates completely when brought into contact with the spinning solution.

The proportion by weight of the polyelectrolyte with negative fixed charges, relative to the weight of the precipitant system used to form the separating layer, is preferably 0.01 to 10 wt.%, and especially preferably 0.05 to 1 wt.%. For values below 0.01 wt.%, no attractive increase of the above-mentioned separation efficiency is observed. For values above 10 wt.%, the solubility of the polyelectrolyte is often insufficient and the ultrafiltration rate of the resulting membrane is reduced.

In step a) of the method of the invention, a spinning solution is prepared that comprises one of the known membrane-forming polymers. The choice of membrane-forming polymer depends, inter al., on the media in which the membrane so produced is to be used. For example, a hydrophobic membrane-forming polymer would be used for a hydrophobic separation medium, and a hydrophilic membrane-forming polymer for a hydrophilic separation medium, to ensure the necessary wetting of the membrane with the respective separation medium. At the same time the membrane-forming polymer must be insoluble in the separation medium.

For production of membranes for hydrophilic separation media, which also include, for example, the media used in hemodialysis, the membrane-forming polymer used in step a) of the method of the invention is preferably a cellulosic polymer, i.e. cellulose or a cellulose derivative such as benzyl cellulose, cellulose diacetate, or cellulose triacetate, or diethylaminoethyl cellulose, or mixtures of these polymers.

In another preferred embodiment of the method of the invention, the membrane-forming polymer used in step a) is a synthetic polymer especially preferably chosen from the group of polysulfones, polyphenylene sulfones, polyethersulfones,

polyaryl ether sulfones, polyimides, polyetherimides, polycarbonates, polyetherketones and polyphenylene sulfides, or from the group of modifications of the cited polymers, or from the group of mixtures of the cited polymers, or from the group of copolymers of the monomers of the cited polymers.

The concentration of the membrane-forming synthetic polymer in the spinning solution conveniently lies in the range 12-30 wt.%, and preferably in the range 15-25 wt.%. Concentrations below 12 wt.% give rise to disadvantages in the execution of the spinning process and in the mechanical stability of the resulting membrane. For concentrations above 30 wt.%, the structure of the resulting membrane is too dense, and the permeability of the membrane therefore too low.

Because the above-mentioned membrane-forming synthetic polymers are, to a greater or lesser extent, markedly hydrophobic, these polymers are suitable for the production of membranes for use in hydrophobic separation media that do not dissolve the membrane.

For production of membranes to be used in hydrophilic separation media, it is possible to use in step a) of the method of the invention either a (co)polymer that is sufficiently wetted as such by the separation medium without dissolving in it, such as a hydrophilic polymer from the group of polyamides, polyvinyl alcohols, ethylene vinyl alcohol copolymers, polyether-polyamide block copolymers, polyethylene oxide polycarbonate block copolymers, or a modified, originally hydrophilic, polymer, such as a polysulfone or polyethersulfone modified with sulfonic acid groups; alternatively, in another preferred embodiment of the method of the invention, the spinning solution can also be produced using in addition a hydrophilic polymer that is, on the one hand, compatible with the membrane-forming polymer and, on the other, ensures that the resulting membrane is sufficiently wettable in the hydrophilic separation medium. Hydrophilic polymers of this type are preferably chosen from the group of polyvinylpyrrolidones, polyethylene glycols, polyvinyl alcohols,

polyglycol monoesters, polysorbates, such as polyoxyethylene sorbitan monooleate, or carboxymethylcellulose. A copolymer of the building blocks of the cited hydrophilic polymers can also be used. Moreover, a mixture of the cited hydrophilic polymers can be used, whereby the polymers can have various molecular weights that differ by, for example, a factor of 5 or more. A polyvinylpyrrolidone is especially preferably used as an additional hydrophilic polymer for preparation of the spinning solution.

In addition to their function of ensuring wetting in the hydrophilic separation medium, the additional hydrophilic polymers used in the production of the spinning solution also have the effect of increasing the viscosity of the spinning solution. Moreover, they can also function as nucleating agents and/or pore-forming agents in the formation of the membrane structure. The hydrophilic polymers that are additionally used are employed in a concentration of 0.1 to 30 wt.%, preferably 1 to 25 wt.%, and especially preferably 5 to 17 wt.%, relative in each case to the weight of spinning solution in step a) of the method of the invention. A significant proportion of the additional hydrophilic polymer is washed out during extraction in step d) of the membrane-production method of the invention. However, on account of the wettability of the resulting membrane that is required in a hydrophilic separation medium, it is essential that a certain proportion of the additional hydrophilic polymer remain in the resulting membrane. This proportion lies preferably in the range 1 to 15 wt.% and especially preferably in the range 3 to 10 wt.%, relative in each case to the weight of the finished membrane.

The solvent system used for production of the spinning solution must be chosen in accordance with the membrane-forming polymer. If, in step a) of the method of the invention, a hydrophobic synthetic polymer is used as the membrane-forming polymer and an additional hydrophilic polymer is used, the solvent system of the invention comprises, for example, polar, aprotic solvents such as ε-caprolactam, dimethylformamide, dimethylacetamide, dimethyl sulfoxide and N-

methylpyrrolidone, or mixtures thereof. Moreover, the solvent system can also contain cosolvents such as, in the case of ε-caprolactam, γ-butyrolactone, propylene carbonate, or a polyalkylene glycol. In addition, the solvent system can also contain non-solvents for the membrane-forming polymer such as water, glycerol, or low-molecular alcohols such as ethanol or isopropanol.

If flat membranes are to be produced by the method of the invention, the spinning solution is converted in step b), after degassing and filtration to remove undissolved particles, into a shaped object with a first surface, i.e. the upper surface, and a second surface, i.e. the lower surface, by means of a known forming device for production of flat membranes, such as a doctor blade. In step c) of the method of the invention the shaped object, with its upper and/or lower surface, is then brought into contact with a precipitant system comprising a polyelectrolyte with negative fixed charges, resulting in the formation of an integrally asymmetric flat membrane having a separating layer on its upper and/or lower surfaces. Finally, in step d), the integrally asymmetric membrane of the method of the invention is washed to remove residues of the solvent system and other dissolved organic components, extracted, and dried if necessary.

The method of the invention is preferably used to produce hollow-fibre membranes. The following remarks therefore refer to the production of hollow-fibre membranes. Those skilled in the art will readily be able to apply the production methods described below to the procedures necessary for flat-membrane production.

In the preferred method for producing hollow-fibre membranes, the forming device used in step b) of the method of the invention is, for example, a conventional hollow-fibre die, through whose annular slit the previously degassed and filtered spinning solution is converted into a hollow-fibre shaped object with an inner surface facing the lumen as the first surface and an outer surface as the second surface.

Moreover, the spinning solution can be converted, in step b), into a hollow-fibre shaped object having a plurality of inner sides.

In a preferred embodiment of the method of the invention, a precipitant system for the membrane-forming polymer is extruded through the central die opening, which is positioned coaxially with the annular slit in the hollow-fibre die, whereby the precipitant system is simultaneously the interior filler that stabilises the lumen of the hollow fibre. After leaving the hollow-fibre die, this precipitant system is brought into contact with the inner surface of the hollow-fibre shaped object in step c), as a result of which an integrally asymmetric hollow-fibre membrane is formed, with the separating layer facing the lumen.

The interior filler comprises one of the previously cited solvents, preferably the solvent that was also used to produce the spinning solution. Alternatively, the interior filler can comprise the solvent system used to produce the spinning solution. In every case the interior filler also contains a non-solvent, which initiates coagulation of the membrane-forming polymer and therefore formation of the lumen-facing separating layer, and which dissolves other hydrophilic polymers that may be present in the spinning solution. If a non-solvent is contained in the solvent system used to produce the spinning solution, the interior filler can contain the same non-solvent, the concentration of the non-solvent in the interior filler naturally being greater than in the solvent system to achieve satisfactory precipitating action. However, it is also possible to use for the interior filler a non-solvent other than that in the solvent system used for preparing the spinning solution. Finally, a mixture of various non-solvents can also be used in the precipitant system. In the method of the invention, the interior filler used in step c) and acting as the precipitant system comprises a polyelectrolyte with negative fixed charges.

Depending on the structure desired for the supporting layer adjoining the lumen-facing separating layer and for the outer surface of the hollow-fibre membrane, the

hollow fibre, in a preferred embodiment of the method of the invention, following its exit from the hollow-fibre die, first traverses an air gap before being immersed in an outer coagulation bath and passed through this. The temperature and relative humidity in the air gap are especially preferably controlled by means of water vapour, to set defined conditions before the start of coagulation on the exterior of the hollow fibre, e.g. through dosed uptake of non-solvent from the conditioned atmosphere, as a result of which slow coagulation occurs. The diffusion-induced coagulation can then be completed in the outer coagulation bath, which is preferably temperature-controlled and preferably an aqueous bath, and the membrane structure can be fixed. If on account of the precipitating action of the interior liquid the hollow fibre is fully precipitated from the interior to the exterior even before immersion in the outer coagulation bath, the function of the outer coagulation bath is limited to fixing the membrane structure and ensuring extraction of the hollow fibre. Instead of using a conditioned air gap that retards coagulation on the outside of the hollow fibre, extrusion can also be carried out directly into an outer coagulation bath that has weaker precipitating action than the interior filler.

In the above embodiments of the method of the invention, the polyelectrolyte with negative fixed charges is added to the interior filler so that an integrally asymmetric hollow-fibre membrane with a lumen-facing separating layer results, which contains the polyelectrolyte with negative fixed charges in physically bound form.

It is, however, also possible, with the method of the invention, to fully precipitate the spinning solution converted into a hollow-fibre shaped object from the outside toward the inside with the help of the outer coagulation bath, whereby the outer coagulation bath contains the dissolved polyelectrolyte with negative fixed charges. In this case an integrally asymmetric hollow-fibre membrane results with an external separating layer containing the physically bound polyelectrolyte with negative fixed charges.

Moreover, it is possible, using the method of the invention, to bring the spinning solution converted into a hollow-fibre shaped object into contact simultaneously with the interior filler as well as the exterior filler, and to coagulate it, whereby a polyelectrolyte with negative fixed charges is dissolved in both the interior filler and the outer coagulation bath. The polyelectrolyte with negative fixed charges in the outer coagulation bath can be the same as that in the interior filler, whereby the polyelectrolyte concentration in the outer coagulation bath and the interior filler lies within the limits cited above, and whereby the polyelectrolyte concentrations in the outer coagulation bath and in the interior filler can be the same or different. Similarly, a polyelectrolyte with negative fixed charges can be dissolved in the outer coagulation bath, this polyelectrolyte being different from the polyelectrolyte with negative fixed charges dissolved in the interior liquid, whereby the concentrations of polyelectrolyte in the outer coagulation bath and the interior liquid lie within the cited limits, and can be the same or different. The resulting integrally asymmetric hollow-fibre membranes have a lumen-facing layer and an external separating layer, the said separating layers containing the same or different physically bound polyelectrolytes with negative fixed charges.

It must in any case be ensured that, in accordance with the teachings of steps b) and c) of the method of the invention, the spinning solution converted into a hollow-fibre shaped object is brought into contact with an interior filler with coagulating action and/or an outer coagulation bath, the interior filler and/or outer coagulation bath containing a polyelectrolyte with negative fixed charges.

Following the coagulation and fixing of the integrally asymmetric structure, the membrane is, in step d) of the method of the invention, extracted, dried if necessary, and textured if necessary, to improve the exchange properties of the hollow fibre membrane in the bundle. Finally, the hollow-fibre membrane is treated by the usual methods, e.g. wound up on a bobbin, or processed into bundles with a suitable filament count and length. The hollow-fibre membranes can also be provided

with accompanying threads, e.g. in the form of multifilament yarns, before production of the bundles, to ensure separation of the hollow-fibre membranes from one another, and allow better flow around individual hollow-fibre membranes.

The object of the invention is further achieved by an integrally asymmetric membrane having at least one separating layer and a supporting layer, characterised in that a polyelectrolyte with negative fixed charges is physically bound in the separating layer.

A membrane of this type surprisingly shows, in comparative with currently known membranes, significantly increased separation efficiency between middle molecules, such as cytochrome c, and high-molecular proteins, such as albumin. In preferred embodiments, which will be described in detail in the examples, the membrane of the invention shows sieving coefficients SC_{CC} for cytochrome c with values above 0.9, and simultaneously sieving coefficients SC_{Alb} for bovine serum albumin with values below 0.003. It is also found that, in addition to the increased selectivity described above, an increased permeability in the form of an increased ultrafiltration rate is also observed in many cases. Moreover, the integrally asymmetric membranes of the invention have improved pyrogen retention.

The membrane of the invention can be in the form of a flat or hollow-fibre membrane, whereby the above description of the method of the invention applies analogously for the polymers forming the membrane, for any additional hydrophilic polymers that may be present, and for the polyelectrolyte with negative fixed charges.

The integrally asymmetric membrane of the invention thus comprises flat membranes with a separating layer on one or both sides and a polyelectrolyte with negative fixed charges contained therein, and hollow-fibre membranes with a lu-

men-facing and/or external separating layer and a polyelectrolyte with negative fixed charges contained therein.

The membrane of the invention is characterised in that the polyelectrolyte with negative fixed charges in the separating layer or layers of the membrane is physically bound. This means that the said polyelectrolyte is not chemically bound in the separating layer of the membrane of the invention. The physical binding of the polyelectrolyte in the separating layer is so stable that neither washing, extraction and sterilisation, which are unavoidable during wet-chemical production of the membrane, nor the use of the membrane of the invention in separation media, such as the typical separation media for hemodialysis, leads to significant loss of polyelectrolyte from the membrane, or to a membrane with no polyelectrolyte content. A tentative explanation is that the polyelectrolyte is securely anchored in the separating layer of the membrane of the invention by interlocking and entanglement between the polymer chains of the polyelectrolyte and those of the membrane-forming polymer, as occurs, for example, during the method of the invention described above by bringing the solvent-moist shaped object formed in step b) into contact, in step c), with the polyelectrolyte-containing precipitant.

In any case, polyelectrolytes with negative fixed charges can be detected in the membranes of the invention, or in the membranes produced by the method of the invention, after their extraction. This evidence for the polyelectrolyte in the separating layer of the membrane is obtained from, e.g., ESCA or IR spectroscopy, such as FTIR-ATR, or by reacting the acid polyelectrolyte with basic dyes. The polyelectrolytes with negative fixed charges that are physically anchored in the separating layer of the membrane of the invention presumably ensure that the integrally asymmetric membrane of the invention shows the same high values of selectivity, e.g. for the cytochrome c / albumin separation, both before and after the extraction process. The same applies to membranes produced by the method of the invention.

In contrast, the use of polyelectrolytes with negative fixed charges in a manner not in accordance with the invention on membranes that are already completely precipitated, where interlocking and entanglement of the polymer chains of the polyelectrolyte with those of the membrane-forming polymer are hardly possible, results in no increase in the separation efficiency.

In a preferred embodiment, the integrally asymmetric membrane of the invention has a supporting layer, adjoining the separating layer, that is free from polyelectrolyte.

In another preferred embodiment, the integrally asymmetric membrane of the invention is a hollow-fibre membrane with lumen-facing separating layer, which is especially preferably 0.1 to 2 μm thick. The method of the invention allows production of integrally asymmetric membranes with separating layer for applications in nanofiltration or ultrafiltration, up to the lower range of microfiltration. The membrane of the invention may therefore be a nanofiltration membrane, an ultrafiltration membrane, or a microfiltration membrane.

The membrane of the invention, or produced by the method of the invention, can advantageously be used for separation of proteins, e.g. for separation of cytochrome c, which, as mentioned above, serves as a marker for β_2-microglobulin, and albumin. The membrane of the invention, or produced by the method of the invention, can therefore advantageously be used in the area of hemodialysis, hemodiafiltration or hemofiltration, particularly as the membranes of the invention often combine their increased selectivity with increased ultrafiltration rates.

Moreover, the membrane of the invention, or produced by the method of the invention, can advantageously be used for chemical modification with an agent that reacts with the polyelectrolyte with negative fixed charges. This allows simple and

specific conversion of chemically inert membranes such as polyethersulfone membranes into affinity membranes.

The invention will now be described in detail with the help of the following examples, in which the following methods have been used for characterisation of the membranes obtained:

Ultrafiltration rate in albumin solution, UFR_{ALB}, sieving coefficients for cytochrome c, SC_{CC}, and albumin, SC_{ALB}.

The above-mentioned membrane properties were measured following DIN 58 353 Part 2. A phosphate buffered saline solution (PBS) containing 50 g/l of bovine serum albumin (BSA) and 100 mg/l of cytochrome c serves as the test solution. The formulation of the PBS solution is from the German Pharmacopoeia (DAB 10.1, Supplement VII.I.3, 1992, Phosphate Buffer Solution pH 7.4, Containing Sodium Chloride R, ["Phosphatpufferlösung pH 7,4, natriumchloridhaltige R"]). The measurement is performed at 37±1°C on hollow-fibre membrane modules with an effective membrane surface area of approx. 250 cm^2 and an effective hollow-fibre membrane length of 180 mm. A flow rate Q_B of 200 ml/(min·m^2) through the hollow-fibre membrane is established by means of a first pump on the inlet side of the membrane module. Via a second, slower, pump on the outlet side of the membrane module a filtrate flow rate is set of Q_F = 30 ml/(min·m^2) or Q_F = 10 ml/(min·m^2), depending on the membrane permeability, i.e. on UFR_{ALB}, a filtrate flow rate Q_F = 10 ml/(min·m^2) being set for a UFR_{ALB} of up to approx. 25 [ml/(h·m^2·mm Hg)]. The transmembrane pressure (TMP) that is established as a result of Q_F is recorded during the measurement.

UFR_{ALB} is calculated from the formula

$UFR_{ALB} = (Q_F \cdot 60) / (TMP \cdot 0.75)$ [ml/(h·m²·mmHg)]

where Q_F is the filtrate flow rate in [ml/(min·m²)] relative to an effective membrane area of 1 m² , and TMP is the transmembrane pressure in [hPa] .

The sieving coefficient SC is determined using the formula

$SC = 2 \cdot c_F / (c_{ST} + c_R)$,

where c_F is the concentration of albumin or cytochrome c in the filtrate, c_{ST} is the original (stock) concentration of the albumin or cytochrome c, i.e. 50 g/l or 100 mg/l, and c_R is the concentration of albumin or cytochrome c in the retentate.

The albumin concentration is determined by a method of Boehringer Mannheim that measures extinction in, e.g., a Hitachi 704 Automatic Analyzer. The test is based on a bromocresol green method, which ensures that the cytochrome c does not affect the analytical measurement.

The cytochrome c concentration is determined by measurement of the extinction E_{415} at λ = 415 nm, which can likewise be carried out in an automatic analyzer such as the Hitachi 704. Because albumin also absorbs at λ=415 nm, the extinction of albumin at λ=415 nm is measured in the concentration range c_{ALB} of 0 to approx. 80 g/l, and the slope m_{ALB415} of the straight line obtained on plotting extinction vs. concentration is determined.

The corrected extinction $E_{415corr}$ corresponding to cytochrome c is determined from the formula

$E_{415corr} = E_{415} - c_{ALB} \cdot m_{ALB415}$

Comparative Example 1

For the preparation of a spinning solution,
19.50 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.65 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
31.75 wt.% of ε-caprolactam,
31.75 wt.% of γ-butyrolactone and
3.35 wt.% of glycerol
are intensively mixed at a temperature of approx. 100°C. The resulting solution is cooled to approx. 60°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 67°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of ε-caprolactam/glycerol/water in the ratio of 61:4:35 by weight is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (approx. 55°C, relative humidity 80%), precipitated and fixed in a coagulation bath containing water maintained at approx. 75°C, washed with water at approx. 90°C and dried. This results in a hollow-fibre membrane with a lumen diameter of approx. 0.2 mm and a wall thickness of approx. 0.03 mm.

Example 1a

A hollow-fibre membrane is produced as in comparative example 1, except that 0.25 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. Acrylidone ACP 1005 is a copolymer of 75% acrylic acid and 25% vinylpyrrolidone. To produce the interior filler, the mixture of ε-caprolactam and water is first prepared, the Acrylidone ACP 1005 is dissolved in this mixture, and glycerol is finally added.

Example 1b

A hollow-fibre membrane is produced as in comparative example 1, except that 0.25 wt.% of the polyelectrolyte Rohagit S hv (from Degussa/Röhm), relative to the weight of interior filler, is also dissolved in the interior filler. Rohagit S hv is a co-polymer of methacrylic acid and methyl methacrylate. To produce the interior filler, the mixture of ε-caprolactam and water is first prepared, the Rohagit S hv is dissolved in this mixture, and glycerol is finally added.

Table 1 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 1 and examples 1a and b.

Table 1

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
comparative example 1	-	37.9	0.009	0.730
Example 1a	0.25 wt.% of ACP 1005	35.1	0.001	0.950
Example 1b	0.25 wt.% of Rohagit S hv	38.7	0.001	0.952

As Table 1 shows, the addition of the polyelectrolytes to the interior filler results in hollow-fibre membranes with considerably increased selectivity for separation of albumin and cytochrome c at approximately the same ultrafiltration rate.

Comparative Example 2

For the preparation of a spinning solution,

19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.68 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
31.98 wt.% of ε-caprolactam,
31.98 wt.% of γ-butyrolactone and
3.36 wt.% of glycerol

are intensively mixed at a temperature of approx. 100°C. The resulting solution is cooled to approx. 60°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 62°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of ε-caprolactam and water in the ratio of 55:45 by weight is extruded through the needle of the hollow-fibre die. The hollow fibre formed is precipitated and fixed in a coagulation bath containing water maintained at approx. 70°C, washed with water at approx. 90°C, and dried. This results in a hollow-fibre membrane with a lumen diameter of approx. 0.2 mm and a wall thickness of approx. 0.035 mm.

Example 2

A hollow-fibre membrane is produced as in comparative example 2, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the mixture of ε-caprolactam and water is first prepared, and the Acrylidone ACP 1005 is dissolved in this mixture.

Table 2 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 2 and example 2.

Table 2

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 2	-	35.2	0.008	0.594
Example 2	0.5 wt.% of ACP 1005	41.6	0.000	0.944

As Table 2 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 3

For the preparation of a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.68 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
31.98 wt.% of ε-caprolactam,
31.98 wt.% of γ-butyrolactone and
3.36 wt.% of glycerol
are intensively mixed at a temperature of approx. 100°C. The resulting solution is cooled to approx. 60°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 62°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of ε-caprolactam/water in the ratio of 55:45 by weight is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (approx. 55°C, relative humidity 80%), precipitated and fixed in a coagulation bath containing water maintained at approx. 55°C, washed with water at approx. 90°C and dried. This results in a hollow-fibre membrane with a lumen diameter of approx. 0.2 mm and a wall thickness of approx. 0.035 mm.

Example 3

A hollow-fibre membrane is produced as in comparative example 3, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is dissolved in the interior filler. To produce the interior filler, the mixture of ε-caprolactam and water is first prepared, and the Acrylidone ACP 1005 is dissolved in this mixture.

Table 3 shows the UFR_{ALB} (Q_F = 10 ml/(min·m²), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 3 and example 3.

Table 3

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 3	-	13.1	0.002	0.305
Example 3	0.5 wt.% of ACP 1005	14.4	0.001	0.846

As Table 3 shows, the addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 4

For the preparation of a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
63.64 wt.% of dimethylacetamide (DMAC) and
4.06 wt.% of water

are intensively mixed at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 40°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 62 parts by weight of DMAC and 38 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), precipitated and fixed in a coagulation bath containing water maintained at approx. 50°C, washed with water at approx. 90°C, and dried at 90°C. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 4

A hollow-fibre membrane is produced as in comparative example 4, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the solvent, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 4 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 4 and example 4.

Table 4

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 4	-	48.0	0.005	0.604
Example 4	0.5 wt.% of ACP 1005	48.9	0.001	0.946

As Table 4 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 5

For the preparation of a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed and dissolved at a temperature of approx. 70°C. The resulting solution is cooled to approx. 60°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 60°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 50 parts by weight of NMP and 50 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), precipitated and fixed in a coagulation bath containing water maintained at approx. 70°C, and then washed and dried. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 5

A hollow-fibre membrane is produced as in comparative example 5, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the solvent, water is then

added, and a homogeneous solution prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 5 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 5 and example 5.

Table 5

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 5	-	42.4	0.006	0.560
Example 5	0.5 wt.% of ACP 1005	42.7	0.002	0.932

As Table 5 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 6

For the preparation of a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
4.75 wt.% of polyvinylpyrrolidone (PVP K90 from ISP),
68.62 wt.% of dimethylacetamide (DMAC) and
7.63 wt.% of glycerol
are intensively stirred at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 47.5 parts by weight of DMAC, 47.5 parts by weight of water and 5 parts by weight of glycerol

is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated and fixed in a coagulation bath containing water maintained at approx. 70°C. The hollow-fibre membrane so obtained is then washed with water at approx. 90°C and dried at approx. 90°C. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 6

A hollow-fibre membrane is produced as in comparative example 6, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the solvent, water is then added, and a homogeneous solution prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 6 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 6 and example 6.

Table 6

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 6	-	36.3	0.003	0.670
Example 6	0.5 wt.% of ACP 1005	35.7	0.002	0.860

As Table 6 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with increased selectivity for separation of albumin and cytochrome c.

Comparative Example 7

For the preparation of a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
4.75 wt.% of polyvinylpyrrolidone (PVP K90 from ISP),
68.62 wt.% of dimethylacetamide (DMAC) and
7.63 wt.% of glycerol
are intensively stirred at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 30 parts by weight of DMAC, 65 parts by weight of water and 5 parts by weight of glycerol is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated and fixed in a coagulation bath containing water maintained at 70°C. The hollow-fibre membrane so obtained is then washed with water at approx. 90°C and dried at approx. 90°C. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 7

A hollow-fibre membrane is produced as in comparative example 7, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the solvent, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 7 shows the UFR_{ALB} (Q_F = 10 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 7 and example 7.

Table 7

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 7	-	11.7	0.002	0.211
Example 7	0.5 wt.% of ACP 1005	12.6	0.001	0.830

As Table 7 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 8

A homogeneous spinning solution is prepared from
19.0 wt.% of polysulfone (Ultrason S 6010 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
65.87 wt.% of N-methylpyrrolidone (NMP) and
1.83 wt.% of water.

For this purpose the polysulfone is first stirred into the greater part of the NMP at a temperature of 70°C and dissolved at 90°C, after which the PVP K30 is added with stirring and likewise dissolved. The resulting solution is cooled to 50°C. The water and the remaining NMP are then added. The resulting solution is degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 40°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 60 parts by weight of NMP and 40 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow

fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated and fixed in a coagulation bath containing water maintained at 70°C The membrane is then washed and dried. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 8

A hollow-fibre membrane is produced as in comparative example 8, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the solvent, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 8 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 8 and example 8.

Table 8

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 8	-	21.0	0.003	0.490
Example 8	0.5 wt.% of ACP 1005	25.0	0.001	0.811

As Table 8 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c, and with even a significant increase in the ultrafiltration rate.

Comparative Example 9

A homogeneous spinning solution is prepared from
19.0 wt.% of polyetherimide (Ultem 1010/1000 from GE),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP), and
67.7 wt.% of N-methylpyrrolidone (NMP).
For this purpose the polyetherimide is first stirred in at a temperature of 70°C and dissolved at 90°C, after which the PVP K30 is added with stirring and likewise dissolved. The solution so obtained is cooled to 50°C. The resulting solution is filtered and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 40°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 75 parts by weight of NMP and 25 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated and fixed in a coagulation bath containing water maintained at 70°C. After washing and drying a hollow-fibre membrane is obtained with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 9

A hollow-fibre membrane is produced as in comparative example 9 , except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the NMP, water is then added, and a homogeneous solution is prepared at approx. 70°C.

Table 9 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 9 and example 9 .

Table 9

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 9	-	36.0	0.003	0.690
Example 9	0.5 wt.% of ACP 1005	30.5	0.001	0.840

As Table 9 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c.

Comparative Example 10

A homogeneous spinning solution is prepared from
19.0 wt.% of polyphenylenesulfone (Radel R 5000NT from Solvay),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
64.32 wt.% of N-methylpyrrolidone (NMP) and
3.38 wt.% of water.
For this purpose the polyphenylenesulfone is first stirred into the greater part of the NMP at a temperature of 70°C and dissolved at 90°C, after which the PVP K30 is added with stirring and likewise dissolved. The resulting solution is cooled to 50°C. The water and the rest of the NMP are then added, and the resulting solution is intensively stirred. The homogeneous solution is degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 63 parts by weight of NMP and 37 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated and fixed in a coagulation bath containing water maintained at 70°C. The membrane is

then washed and dried. This results in a hollow-fibre membrane with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 10

A hollow-fibre membrane is produced as in comparative example 10, except that 0.5 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler. To produce the interior filler, the Acrylidone ACP 1005 is first dispersed in the NMP, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 10 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 10 and example 10 .

Table 10

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 10	-	30.7	0.001	0.470
Example 10	0.5 wt.% of ACP 1005	33.3	0.000	0.840

As Table 10 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with considerably increased selectivity for separation of albumin and cytochrome c, and with even a slight increase in the ultrafiltration rate.

Comparative Example 11

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 55°C, degassed, filtered at 55 °C, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 54 parts by weight of NMP and 46 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%) and precipitated in a coagulation bath containing water maintained at approx. 70°C. After washing with water at approx. 85°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Examples 11a-e

Hollow-fibre membranes are produced as in comparative example 11, except that 0.01 to 0.25 wt.% of the polyelectrolyte Rohagit S hv (from Degussa / Röhm), relative to the weight of interior filler, is also dissolved in the interior filler in each case. To prepare the interior filler in each case, the Rohagit S hv is first dispersed in the NMP, dissolved after addition of water at approx. 70°C, and then cooled to 30°C.

Table 11 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 11 and examples 11a-e.

Table 11

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 11	-	31.5	0.003	0.640
Example 11a	0.01 wt.% of Rohagit S hv	32.9	0.002	0.820
Example 11b	0.025 wt.% of Rohagit S hv	32.7	0.001	0.935
Example 11c	0.05 wt.% of Rohagit S hv	31.1	0.001	0.960
Example 11d	0.1 wt.% of Rohagit S hv	33.1	0.001	0.970
Example 11e	0.25 wt.% of Rohagit S hv	32.9	0.001	0.970

As Table 11 shows, the addition of the polyelectrolyte to the interior filler results in hollow-fibre membranes with considerably increased selectivity for the separation of albumin and cytochrome c.

Comparative Example 12

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 54 parts by weight of NMP and 46 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a

coagulation bath containing water maintained at approx. 63°C. After washing with water at 85°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.03 mm.

Examples 12a-e

Hollow-fibre membranes are produced as in comparative example 12, except that 0.01 to 0.25 wt.% of the polyelectrolyte Rohagit S ENV (from Degussa / Röhm), relative to the weight of interior filler, is also dissolved in the interior filler in each case. Rohagit S ENV is a copolymer of methacrylic acid and methyl methacrylate. To prepare the interior filler in each case, the Rohagit S ENV is first dispersed in the NMP, dissolved after addition of water at approx. 70°C, and then cooled to 30°C.

Table 12 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 12 and examples 12a-e.

Table 12

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 12	-	28.9	0.002	0.640
Example 12a	0.01 wt.% of Rohagit S ENV	26.5	0.002	0.690
Example 12b	0.025 wt.% of Rohagit S ENV	28.3	0.001	0.800
Example 12c	0.05 wt.% of Rohagit S ENV	28.3	0.001	0.875
Example 12d	0.1 wt.% of Rohagit S ENV	27.0	0.000	0.880
Example 12e	0.25 wt.% of Rohagit S ENV	27.3	0.001	0.890

As Table 12 shows, addition of the polyelectrolyte to the interior filler results in hollow-fibre membranes with considerably increased selectivity for the separation of albumin and cytochrome c, the ultrafiltration rate being somewhat reduced.

Comparative Example 13

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 54 parts by weight of NMP and 46 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a coagulation bath containing water maintained at approx. 67°C. After washing with water at 85°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Examples 13a-e

Hollow-fibre membranes are produced as in comparative example 13, except that 0.01 to 0.25 wt.% of the polyelectrolyte Acrylidone ACP 1005 (from ISP), relative to the weight of interior filler, is also dissolved in the interior filler in each case. To produce the interior filler in each case, the Acrylidone ACP 1005 is first dispersed

in the solvent, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 13 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 13 and examples 13a-e.

Table 13

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 13	-	36.1	0.002	0.632
Example 13a	0.01 wt.% of ACP 1005	42.5	0.004	0.784
Example 13b	0.025 wt.% of ACP 1005	40.1	0.005	0.830
Example 13c	0.05 wt.% of ACP 1005	39.6	0.005	0.889
Example 13d	0.1 wt.% of ACP 1005	38.8	0.001	0.912
Example 13e	0.25 wt.% of ACP 1005	33.6	0.000	0.968

As Table 13 shows, addition of the polyelectrolyte to the interior filler results in hollow-fibre membranes with considerably increased selectivity for separation of albumin and cytochrome c, with the ultrafiltration rate, except for Acrylidone ACP 1005 in a proportion of 0.25 wt.%, being actually higher than in the absence of the polyelectrolyte.

Comparative Examples 14a-f

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water

are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, filtered, degassed, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of NMP and water is extruded through the needle of the hollow-fibre die. Six different membranes are produced, the composition of the interior filler being varied stepwise with the NMP:water ratio ranging between 48:52 and 58:42 wt.%. The hollow fibre formed in each case is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a coagulation bath containing water maintained at approx. 70°C. After washing with water at 80°C and drying in hot air, hollow-fibre membranes result with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Examples 14a-f

Hollow-fibre membranes are produced as in comparative examples 14a-f, except that 0.1 wt.% of the polyelectrolyte Rohagit S hv (from Degussa / Röhm), relative to the weight of interior filler, is also dissolved in the interior filler in each case. To prepare the interior filler in each case, the Rohagit S hv is first dispersed in the NMP, dissolved after addition of water at approx. 70°C, and then cooled to 30°C.

Table 14 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative examples 14a-f and examples 14a-f.

Table 14

Membrane from	NMP:water	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 14a	48:52	26.3	0.001	0.550
Comparative example 14b	50:50	33.7	0.003	0.660
Comparative example 14c	52:48	36.5	0.009	0.740
Comparative example 14d	54:46	42.4	0.027	0.780
Comparative example 14e	56:44	45.9	0.047	0.810
Comparative n example 14f	58:42	57.8	0.075	0.860
Example 14a	48:52	24.0	0.001	0.960
Example 14b	50:50	30.0	0.000	0.920
Example 14c	52:48	33.1	0.001	0.980
Example 14d	54:46	42.5	0.002	0.980
Example 14e	56:44	47.5	0.001	0.970
Example 14f	58:42	52.4	0.000	0.950

Table 14 shows that membranes having the same NMP:water ratio show considerably higher selectivity for separation of albumin and cytochrome c if just 0.1 wt.% of the polyelectrolyte Rohagit S hv is added to the interior filler during membrane production.

Comparative Example 15

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 52 parts by weight of NMP and 48 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a coagulation bath containing water maintained at approx. 75°C. After washing with water at 80°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 15

A hollow-fibre membrane is produced as in comparative example 15, except that 0.25 wt.% of the polyelectrolyte Rohagit ENV (from Degussa/Röhm), relative to the weight of interior filler, is also dissolved in the interior filler. To prepare the interior filler, the Rohagit S ENV is first dispersed in the NMP, dissolved after addition of water at approx. 70°C, and then cooled to 30°C.

Table 15 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 15 and example 15 .

Table 15

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 15	-	31.5	0.003	0.640
Example 15	0.25 wt.% of Rohagit ENV	35.1	0.000	1.000

As Table 15 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with the best possible selectivity for separation of albumin and cytochrome c.

Comparative Example 16

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 56 parts by weight of NMP and 44 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a coagulation bath containing water maintained at approx. 75°C. After washing with water at 80°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.035 mm.

Example 16

A hollow-fibre membrane is produced as in comparative example 16 except that 0.1 wt.% of the polyelectrolyte Carbopol 980 (from Noveon), relative to the weight of interior filler, is also dissolved in the interior filler. Carbopol 980 is a partially crosslinked acrylic acid. To produce the interior filler, the Carbopol 980 is first dispersed in the NMP, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 16 shows the UFR_{ALB} (Q_F = 30 ml/(min·m²), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 16 and example 16.

Table 16

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 16	-	60.6	0.065	0.780
Example 16	0.1 wt.% of Carbopol 980	55.9	0.014	0.902

As Table 16 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with significantly increased selectivity for separation of albumin and cytochrome c, and a decrease in the ultrafiltration rate.

Comparative Example 17

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively mixed in a stirring vessel at a temperature of approx. 70°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 52 parts by weight of NMP and 48 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (50°C, relative humidity 90%), and precipitated in a coagulation bath containing water maintained at approx. 70°C. After washing with water at 80°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.036 mm.

Example 17

A hollow-fibre membrane is produced as in comparative example 17 except that 0.075 wt.% of the polyelectrolyte Carbopol 1382 (from Noveon), relative to the weight of interior filler, is also dissolved in the interior filler. Carbopol 1382 is a partially crosslinked acrylic acid. To produce the interior filler, the Carbopol 1382 is first dispersed in the NMP, water is then added, and a homogeneous solution is prepared at approx. 70°C. The solution is finally cooled to 30°C.

Table 17 shows the UFR_{ALB} (Q_F = 10 ml/(min·m²)), SC_{CC} and SC_{ALB} of the hollow-fibre membranes of comparative example 17 and example 17.

Table 17

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml (h·m²·mmHg)	SC_{ALB}	SC_{CC}
Comparative example 17	-	20.2	0.003	0.350
Example 17	0.075 wt.% of Carbopol 1382	23.2	0.001	0.658

As Table 17 shows, addition of the polyelectrolyte to the interior filler results in a hollow-fibre membrane with significantly increased selectivity for separation of albumin and cytochrome c, and an increase in the ultrafiltration rate.

Example 18

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively stirred at a temperature of approx. 60°C. The resulting solution is cooled to approx. 50°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 52 parts by weight of NMP and 48 parts by weight of water, and with an addition of 0.1 wt.%, relative to the weight of interior filler, of the polyelectrolyte Carbopol 1382 (from Noveon) is extruded through the needle of the hollow-fibre die. To produce the interior filler, the Carbopol 1382 is first dispersed in NMP and then dissolved after addition of water at approx. 70°C. The hollow fibre formed is conducted through a

conditioning channel (55°C, relative humidity 80%), and precipitated in a coagulation bath containing water maintained at approx. 71°C. After washing with water at 90°C and drying in hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.03 mm, of which the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} are shown in Table 18.

Table 18

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Example 18	0.1 wt.% of Carbopol 1382	35.82	0.002	0.956

Examples 19a-b

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively stirred at a temperature of approx. 60°C. The resulting solution is degassed at 60°C, filtered and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, interior fillers consisting respectively of 55.95 parts by weight of NMP and 43.95 parts by weight of water, with an addition of 0.1 wt.% of the polyelectrolyte Styleze 2000 (from ISP) (example 19a), and of 55.88 parts by weight of NMP and 43.88 parts by weight of water, with an addition of 0.25 wt.% of Styleze 2000 (example 19b) are extruded through the needle of the hollow-fibre die. To produce the interior filler, the Styleze 2000 is first stirred into the NMP and then dissolved after addition of water at approx. 70°C. Styleze 2000 is a copolymer

of acrylic acid, vinylpyrrolidone and lauryl methacrylate. The hollow fibre formed is conducted through a conditioning channel (55°C, relative humidity 70%), and precipitated in a coagulation bath containing water maintained at approx. 69°C After washing with water at 90°C and drying in hot air, hollow-fibre membranes result with a lumen diameter of 0.2 mm and a wall thickness of 0.03 mm, of which the UFR_{ALB} (Q_F = 30 ml/(min·m²)), SC_{CC} and SC_{ALB} are shown in Table 19.

Table 19

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} ml/(h·m²·mmHg)	SC_{ALB}	SC_{CC}
Example 19a	0.1 wt.% of Styleze 2000	36.04	0.001	0.931
Example 19b	0.25 wt.% of Styleze 2000	38.09	0.001	0.937

Comparative Example 20

To prepare a spinning solution,
19.0 wt.% of polyethersulfone (Ultrason E 6020 from BASF),
13.3 wt.% of polyvinylpyrrolidone (PVP K30 from ISP),
62.96 wt.% of N-methylpyrrolidone (NMP) and
4.74 wt.% of water
are intensively stirred at a temperature of approx. 60°C. The resulting solution is cooled to approx. 60°C, degassed, filtered, and conveyed to the annular slit of a hollow-fibre die that is maintained at a temperature of 45°C. For the formation of the lumen and the inner separating layer, an interior filler consisting of 44 parts by weight of NMP and 56 parts by weight of water is extruded through the needle of the hollow-fibre die. The hollow fibre formed is conducted through a conditioning channel (55°C, relative humidity 70%), and precipitated in a coagulation bath containing water maintained at 58°C. After washing with water at 90°C and drying in

hot air, a hollow-fibre membrane results with a lumen diameter of 0.2 mm and a wall thickness of 0.03 mm.

Example 20

A hollow-fibre membrane is produced as in comparative example 20, except that the interior filler consists of 43.88 parts by weight of NMP and 55.88 parts by weight of water, with the addition of 0.25 wt.% of Styleze 2000.

Table 20 shows the UFR_{ALB} (Q_F = 10 ml/(min·m²), SC_{CC} and SC_{ALB} of the membranes of comparative example 20 and example 20.

Table 20

Membrane from	Polyelectrolyte in the interior filler	UFR_{ALB} $\frac{ml}{(h \cdot m^2 \cdot mmHg)}$	SC_{ALB}	SC_{CC}
Comparative example 20	-	12.28	0.003	0.129
Example 20	0.25 wt.% of Styleze 2000	11.04	0.002	0.784

Integrally Asymmetric Membrane, Method for its Production, and its Use

Claims

1. A method for production of an integrally asymmetric membrane with at least one separating layer and a supporting layer adjoining the separating layer, comprising the steps
   a) preparation of a spinning solution comprising a membrane-forming polymer and a solvent system,
   b) conversion of the spinning solution by means of a forming device into a shaped object
   with a first and a second surface,
   c) bringing of the first and/or second surface into contact with a precipitant system, resulting in the formation of a membrane having a separating layer on the first and/or second surface, and
   d) washing and, if necessary, drying of the membrane,
   characterised in that in step c) the precipitant system comprises a polyelectrolyte with negative fixed charges.

2. Method according to Claim 1, characterised in that the polyelectrolyte with negative fixed charges is chosen from the group of polyphosphoric acids, poly-

sulfonic acids or polycarboxylic acids.

3. Method according to Claim 2, characterised in that the polycarboxylic acids are homo- or copolymers of acrylic acid

4. Method according to one or more of Claims 1 to 3, characterised in that the polyelectrolyte dissolved in the precipitant system precipitates in contact with the spinning solution.

5. Method according to one or more of Claims 1 to 4, characterised in that the proportion by weight of the polyelectrolyte with negative fixed charges, relative to the weight of the precipitant system, is 0.01 to 10 wt.%.

6. Method according to Claim 5, characterised in that the proportion by weight of the polyelectrolyte with negative fixed charges, relative to the weight of the precipitant system, is 0.05 to 1 wt.%.

7. Method according to one or more of Claims 1 to 6, characterised in that in step a) a cellulosic polymer is used as the membrane-forming polymer.

8. Method according to one or more of Claims 1 to 6, characterised in that in step a) a synthetic polymer is used as the membrane-forming polymer.

9. Method according to Claim 8, characterised in that the synthetic polymer is chosen from the group of polysulfones, polyphenylene sulfones, polyethersulfones, polyaryl ether sulfones, polyimides, polyetherimides, polycarbonates, polyetherketones and polyphenylene sulfides, or from the group of modifications of the cited polymers, or from the group of mixtures of the cited polymers, or from the group of copolymers of the monomers of the cited polymers.

10. Method according to one or more of Claims 1 to 9, characterised in that in step b) the forming device used is a hollow-fibre die, which converts the spinning solution into a hollow-fibre shaped object with an inner surface as the first surface and an outer surface as the second surface.

11. Method according to Claim 10, characterised in that in step c) the precipitant system is an interior filler that is brought into contact with the inner surface, resulting in the formation of a membrane with a separating layer facing the lumen.

12. Integrally asymmetric membrane with at least one separating layer and a supporting layer, characterised in that a polyelectrolyte with negative fixed charges is physically bound in the separating layer.

13. Membrane according to Claim 12, characterised in that the supporting layer is free from polyelectrolyte.

14. Membrane according to Claim 12 or 13, characterised in that the membrane is a hollow-fibre membrane with a separating layer facing the lumen.

15. Use of the membrane produced according to one or more of Claims 1 to 11, or of the membrane according to one or more of Claims 12 to 14, for separation of proteins.

16. Use of the membrane produced according to one or more of Claims 1 to 11, or of the membrane according to one or more of Claims 12 to 14, for chemical modification with an agent that reacts with the polyelectrolyte with negative fixed charges.

Integrally Asymmetric Membrane, Method for its Production, and its Use

Abstract

A method for production of an integrally asymmetric membrane with at least one separating layer and a supporting layer adjoining the separating layer comprises the steps

a) preparation of a spinning solution comprising a membrane-forming polymer and a solvent system,
b) conversion of the spinning solution by means of a forming device into a shaped object with a first and second surface,
c) bringing of the first and/or second surface into contact with a precipitant system, resulting in the formation of a membrane having a separating layer on the first and/or second surface,
d) washing and, if necessary, drying of the membrane,

whereby the precipitant system in step c) comprises a polyelectrolyte with negative fixed charges. In comparative with membranes produced by known methods, the membrane of the invention shows significantly increased separation efficiency between middle molecules, such as cytochrome c, and high-molecular proteins, such as albumin.

Attorney Docket No. 2037.6 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Wechs Art Unit:

Serial No. 10/588,016 Examiner:

Filed: August 1, 2006

For: HIGH-FLUX DIALYSIS MEMBRANE WITH IMPROVED SEPARATION BEHAVIOUR

PRELIMINARY AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Preliminary Amendment is being filed along with a Petition under Rule 182 that requests, among other things, entry of the correct translation of the priority document.

Amendment to the claims begins on page 2.

Remarks begin on page 7.

Amendment to the claims

Kindly enter the following amendments to the claims:

1. (original) A method for production of an integrally asymmetric membrane with at least one separating layer and a supporting layer adjoining the separating layer, comprising the steps

a) preparation of a spinning solution comprising a membrane-forming polymer and a solvent system,

b) conversion of the spinning solution by means of a forming device into a shaped object with a first and a second surface,

c) bringing of the first and/or second surface into contact with a precipitant system, resulting in the formation of a membrane having a separating layer on the first and/or second surface, and

d) washing and, if necessary, drying of the membrane,

characterised in that in step c) the precipitant system comprises a polyelectrolyte with negative fixed charges.

2. (currently amended) The method ~~Method~~ according to Claim 1, characterised in that the polyelectrolyte with negative fixed charges is chosen from the group of polyphosphoric acids, polysulfonic acids or polycarboxylic

acids.

3. (currently amended) The method ~~Method~~ according to Claim 2, characterised in that the polycarboxylic acids are homo- or copolymers of acrylic acid

4. (currently amended) The method ~~Method~~ according to ~~one or more of~~ Claim~~s~~ 1 ~~to 3~~, characterised in that the polyelectrolyte dissolved in the precipitant system precipitates in contact with the spinning solution.

5. (currently amended) The method ~~Method~~ according to ~~one or more of~~ Claim~~s~~ 1 ~~to 4~~, characterised in that the proportion by weight of the polyelectrolyte with negative fixed charges, relative to the weight of the precipitant system, is 0.01 to 10 wt.%.

6. (currently amended) The method ~~Method~~ according to Claim 5, characterised in that the proportion by weight of the polyelectrolyte with negative fixed charges, relative to the weight of the precipitant system, is 0.05 to 1 wt.%.

7. (currently amended) The method ~~Method~~ according to ~~one or more of~~ Claims ~~1 to 6~~, characterised in that in step a) a cellulosic polymer is used as the membrane-forming polymer.

8. (currently amended) The method ~~Method~~ according to ~~one or more of~~ Claims ~~1 to 6~~, characterised in that in step a) a synthetic polymer is used as the membrane-forming polymer.

9. (currently amended) The method ~~Method~~ according to Claim 8, characterised in that the synthetic polymer is chosen from the group of polysulfones, polyphenylene sulfones, polyethersulfones, polyaryl ether sulfones, polyimides, polyetherimides, polycarbonates, polyetherketones and polyphenylene sulfides, or from the group of modifications of the cited polymers, or from the group of mixtures of the cited polymers, or from the group of copolymers of the monomers of the cited polymers.

10. (currently amended) The method ~~Method~~ according to ~~one or more of~~ Claims ~~1 to 9~~, characterised in that in step b) the forming device used is a hollow-fibre die, which converts the spinning solution into a hollow-fibre

shaped object with an inner surface as the first surface and an outer surface as the second surface.

11. (currently amended) The method ~~Method~~ according to Claim 10, characterised in that in step c) the precipitant system is an interior filler that is brought into contact with the inner surface, resulting in the formation of a membrane with a separating layer facing the lumen.

12. (currently amended) An integrally ~~Integrally~~ asymmetric membrane with at least one separating layer and a supporting layer, characterised in that a polyelectrolyte with negative fixed charges is physically bound in the separating layer.

13. (currently amended) The integrally asymmetric membrane ~~Membrane~~ according to Claim 12, characterised in that the supporting layer is free from polyelectrolyte.

14. (currently amended) The integrally asymmetric membrane ~~Membrane~~ according to Claim 12 ~~or 13~~, characterised in that the membrane is a hollow-fibre

membrane with a separating layer facing the lumen.

15. (currently amended) ~~Use of the membrane produced according to one or more of Claims 1 to 11, or of the membrane~~ The integrally asymmetric membrane according to ~~one or more of~~ Claim~~s~~ 12 ~~to 14~~, wherein the membrane being for separation of proteins.

16. (currently amended) ~~Use of the membrane produced according to one or more of Claims 1 to 11, or of the membrane~~ The integrally asymmetric membrane ~~Membrane~~ according to ~~one or more of~~ Claims 12 ~~to 14~~, wherein the membrane being for chemical modification with an agent that reacts with the polyelectrolyte with negative fixed charges.

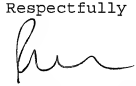
Remarks

Consideration and allowance of the instant application is respectfully requested based upon the amended claims set out above.

The claim amendments are directed to the correct translation submitted the **Petition under Rule 182** (submitted simultaneously herewith).

An early Notice of Allowance is respectfully requested.

Respectfully submitted,



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